REMARKS

Reconsideration of this application and entry of this amendment are solicited. Please be advised that concurrently with this Amendment and Notice of Appeal was also filed in order to maintain pendency of this application and secure consideration of this response.

Claims 1-9 and 10-14 will be present in the application subsequent to entry of this amendment.

In order to more particularly point out and distinctly claim the subject matter that we regard as the present invention, the following amendments claims 1, 2, and 8 are proposed. To derive these amended claims, wording from lines 1-3 of claim 9 is inserted in each of claims 1, 2, and 8. Claim 9 has been canceled, the dependencies on claim 9 in claims 10, 11, 12, and 13 have been deleted, and claim 15 has been canceled because it was solely dependent on claim 9. No new matter has been added to the amended claims.

Claims 1-7 were rejected as being "obvious" over Duclos et al in view of Ecanow while remaining claims 8-15 were rejected on the same grounds over the same two references further in combination with Haynes. These rejections are respectfully traversed having regard to the above claim amendments and following comments.

Applicants' claims are patentably distinct from the cited documents. The "solid dispersions" consisting of a "co-precipitate of therapeutic agent and hydrophilic polymer" of Duclos et al. (see U.S. Patent 5,776,495, abstract) are different from the compositions of the current invention for the following reason. The solid dispersions of Duclos et al. consist of particles connected to one another by a very hydrophilic polymer, i.e., the particles are aggregated. As the examiner knows, "aggregated" is commonly defined as "gathered together into a mass constituting a whole" [see page 86 of Webster's II New Riverside University Dictionary, Houghton Mifflin Co., Boston, MA (1984)]. However, in the composition of the current invention the particles are not aggregated. The phospholipid and surfactant prevent "particles from aggregating or flocculating by coating or adhering onto the surfaces of the fenofibrate particles" (see

the current application, amended claims 1 and 2, and the process for the preparation of such particles in claim 8).

In this regard, Duclos et al. (U.S. Patent 5,776,495) disclose a process "for the production of a solid dispersion of at least one therapeutic agent in a hydrophilic carrier having enhanced solubility in an aqueous media" which "comprises dissolving at least one therapeutic agent in a volatile organic solvent containing a very hydrophilic polymer and evaporating the solvent to dryness to form a co-precipitate of therapeutic agent and hydrophilic polymer" (see column 2, lines 21-24). Duclos et al. also teach "the solid dispersions are systems in which one or several active ingredients are dispersed in the solid state (microparticular, even molecular) in an inert solid vehicle" (see column 2, lines 55-58). Duclos et al also disclose "the co-precipitates also show the appearance of a white, crumbly and easily recoverable foam" (see column 6, lines 59-60); "the co-precipitate which appeared in the form of a very stable white foam was easily recoverable by scratching the bottom of the flask with a spatula" (see column 7, lines 55-57); "co-precipitates obtained before staying in the exsiccator were in the form of a crystalline block, pale yellow or white, and small crystalline clusters were also recovered" (see column 15, lines 60-62); and "the Samples with 2.5 g of fenofibrate had a yellowish appearance and formed a pellet more or less viscous, after one hour of evaporation at the minimal pressure" (see column 17, lines 22-25). Pellets and foams have structural integrity and exist because of connective interactions or molecular associations of their components such as a hydrophilic polymer in the form of a matrix. Particles within a pellet and within a foam are aggregated because of the interconnections.

The coacervate of Ecanow disclosed in US Patent 4,963,367 also provides an material in the form of a matrix: "... the compositions of the present invention are derived from a non-toxic two-phase aqueous coacervate system forming a matrix containing at least on polymerized surface active compound ..." (see Ecanow, column 7, lines 31-34), and that the coacervate phase is "capable of solubilizing (holding within the coacervate matrix) oil-soluble and water-insoluble components" (see Ecanow, column 7, lines 34-37). The method of Ecanow uses "non-toxic aqueous coacervate; said method produces stable microemulsions comprised of particles in which one or

more pharmaceutical components have been incorporated" (see Ecanow, column 1, line 54-57).

Microemulsions are well known in the art to be liquid droplets rather than solid particles whereas the current invention defines "Microparticles, as used herein, refer to solid fenofibrate particles of irregular, non-spherical or spherical shapes with combinations of natural and synthetic phospholipids, and one or more nonionic, anionic or cationic surfactants coated or adhered onto the surfaces of the fenofibrate particles" (see page 3, lines 19-22). Ecanow also teaches "In this invention, the pharmacologically-active component is bound to or embedded in the coacervate matrix..." (see column 5, lines 61-63) and that "the drug is solubilized in (held within the matrix of) the colloid-rich phase of the composition" (see column 13, lines 12-14). The coacervates of Ecanow do not comprise "phospholipid and surfactant preventing fenofibrate particles from aggregating or flocculating by coating or adhering onto the surfaces of the particles" in the manner of the current invention. Thus, they are quite different from the current invention where the drug is not dissolved in either an organic solvent or in a coacervate phase.

The advantages of the 50% reduction in size of the fenofibrate particles are described in the current disclosure: "microparticulate formulations exhibit enhanced stability and bioavailability" (see page 4, line 18-19); "suppressing the process of Ostwald Ripening and therefore maintaining the particle size" (see page 7, lines 3-4); "increasing the storage stability, minimizing sedimentation, and decreasing the particle growth during lyophilization and reconstitution" (page 7, lines 4-7); and "... the pharmacokinetic results ... demonstrate the superior bioavailability of the fenofibrate formulation over the commercially available product" (see Example A).

The product and process of the current invention are different from those described in the prior art, and thus disclose a unique composition and a unique composition produced by a unique process. The process of the current invention provides particles of a size 50% smaller than fenofibrate particles prepared for example by the method of Haynes using phospholipids alone without the additional surface modifier used in the process of the current invention.

The current process is an improvement of the process disclosed in Haynes applied to fenofibrate. In the current invention, the phospholipid and the surfactant are present at the time of formation of the fenofibrate microparticles by a given energy input, and the phospholipid and the surfactant prevent the particles from aggregating or flocculating by coating or adhering onto the surfaces of the fenofibrate particles. Because of the 50% reduction in size, and the well-known mathematical relationship between volume and surface area, a reduction in particle size provides microparticles with smaller amounts of fenofibrate inside each particle relative to larger particles prepared using phospholipid alone with the same energy input, while the surface area is reduced non-linearly with respect to the volume change. Concomitant with this is a necessary change in the amount of phospholipid that is adsorbed to the surface per unit area to accommodate both the smaller surface area and the presence of additional surfactant.

For a given amount of phospholipid and fenofibrate, the composition of phospholipid plus surfactant both of which are adsorbed at the surface of the fenofibrate particles must be quite different than that in which phospholipid alone is present on the surface, and quite different from that hypothetical situation where phospholipid is coated on the surface and a surfactant is coated or otherwise associated on the phospholipid.

The particles of the current invention are reduced in size and stabilized versus particles prepared with phospholipid alone at a given same energy input level involved in the particle reduction. The reduction in size of the particle is a result of additional particle stabilizing energy arising from the combination of phospholipid and surfactant, both adsorbed on the microparticle surface. Changing the manner in which the phospholipid and surfactant associate with the fenofibrate surface area changes the stabilization energy provided by those molecules at the surface of the particle. This leads to a change in the particle size that is stabilized by the combination of surface modifiers. The compositions of Duclos, of Ecanow, and of Haynes (US 5,091,187 which requires a membrane-forming stabilizer that specifically excludes surfactants) are different from the compositions of the current invention. Thus, the surface energies available to stabilize the respective particles will be different and would not be expected to provide the same size range as that of the current invention.

The use of the surface active agents and phospholipids taught in Ecanow in the process of Duclos is expected to provide a composition of Duclos which as shown above is different from the composition of the current invention. Different compositions are expected because Duclos does not teach that the phospholipid and surfactant prevent particles from aggregating or flocculating by coating or adhering onto the surfaces of the fenofibrate particles. Rather, Duclos teaches that the fenofibrate should be in an aggregate foam or matrix that is different from the current invention. Furthermore, the change in particle size over that expected from the method of Haynes (which cannot use a surfactant because it does not form a membrane) by a 50% reduction using the same energy input suggests a different and unexpected surface energy profile for the particles of the current invention that reflects a novel combination of surface active agents applied to the surface of the particles in a stabilizing fashion. The current process is an improvement of the process of Haynes, and the combination of components is novel over that produced by Haynes, Duclos, and Ecanow.

For the above reasons it is respectfully submitted the claims of this application define subject matter that is patentable over the prior art cited. Reconsideration, entry of this amendment and favorable action are solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page(s) is captioned "**Version With Markings To Show Changes Made**."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

1. (Amended) A pharmaceutical composition comprising fenofibrate containing microparticles produced by applying energy to fenofibrate in the presence of phospholipid and surface modifier(s), said microparticles consisting essentially of fenofibrate, a phospholipid and at least one surface modifier preventing particles from aggregating or flocculating by coating or adhering onto the surfaces of the fenofibrate particles in which the surface modifier or surface modifiers provide volume-weighted mean particle size values of the water-insoluble compound about 50% smaller than particles produced in the presence of a phospholipid and without the presence of the surface modifier using the same energy input.

2. (Amended) A pharmaceutical composition comprising fenofibrate containing microparticles produced by applying energy to fenofibrate in the presence of phospholipid and surfactant surface modifier, said microparticles consisting essentially of fenofibrate, a phospholipid and at least one non-ionic, anionic or cationic surfactant, said phospholipid and surfactant preventing particles from aggregating or flocculating by coating or adhering onto the surfaces of the fenofibrate particles , in which the surfactant or surfactants provide volume-weighted mean particle size values of the water-insoluble compound about 50% smaller than particles produced in the presence of a phospholipid and without the presence of the surfactant using the same energy input.

8. (Amended) In a process of preparing fenofibrate microparticles comprising reducing the particle size by sonication, homogenization, milling, microfluidization and

precipitation, or recrystallization and precipitation of the fenofibrate using antisolvent and solvent precipitation or precipitation from supercritical fluids, the improvement comprising the steps of:

(1) prior to or during particle size reduction, mixing the fenofibrate particles with (a) a natural or synthetic phospholipid and (b) at least one non-ionic, anionic or cationic surfactant, and thereafter

(2) applying energy to the mixture sufficient to produce volume-weighted mean particle size values of fenofibrate about 50% smaller than particles produced without the presence of the surfactant using the same energy input with said phospholipid and surfactant preventing said produced particles from aggregating or flocculating by coating or adhering onto the surfaces of the fenofibrate particles .

10. (Amended) The process of claim 8 [or 9] wherein the phospholipid is of egg or plant origin or semisynthetic or synthetic in partly or fully hydrogenated form or in a desalted or salt form such as phosphatidylcholine, or dimyristoyl phosphatidylglyerol sodium, salt, phosphatidylethanolamine, phosphatidiylserine, phosphatidic acid, lysophospholipids, or combinations thereof.

11. (Amended) The process of claim 8 [or 9] wherein the surfactant is a polyoxyethylene sorbitan fatty acid ester polyoxyethylene stearate, a block copolymer of ethylene oxide and propylene oxide, a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine, an alkyl aryl polyether sulfonate, polyethylene glycol, hydroxy propylmethylcellulose, sodium dodecylsulfate, sodium deoxycholate, cetyltrimethylammonium bromide or combinations thereof.

12. (Amended) The process of claim 8 [or 9] wherein at least two surfactants are used.

13. (Amended) The process of claim 8 [or 9] wherein the surfactant is present above the critical micelle concentration.